Acute leukemia

- Aggressive malignant hematopoietic disorders
- Accumulation of abnormal blasts (Immature precursors of WBC)

  in bone marrow and blood leading to:

  1- Bone marrow failure (anemia ,neutropenia & thrombocytopenia)

  2- Organ infiltration (hepatosplenomegy ,lymphadenopathy)

HISTORY

- Means “white blood” in Greek.
- Named by pathologist Virchow in 1845.
- Classified by FAB classification systems in 1976.
- Reclassified by World Health Organization in 2001 & 2008.

PATHOGENESIS

Genetic predisposition

Environmental factors

Infection

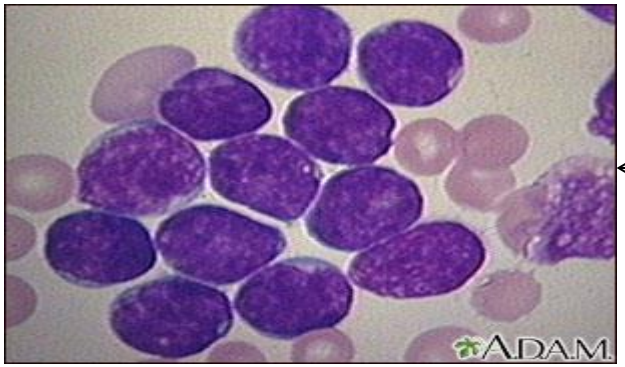
Previous therapy

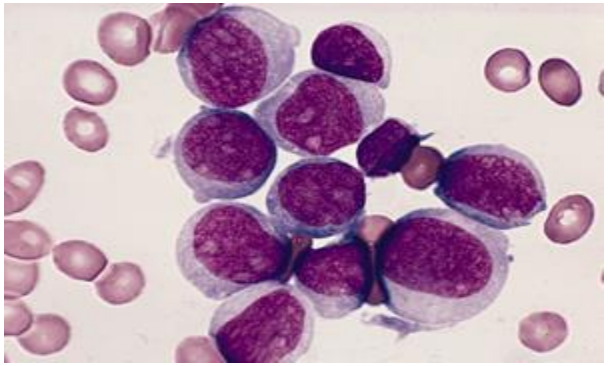
Other hematological disorders

Unknown Mechanism

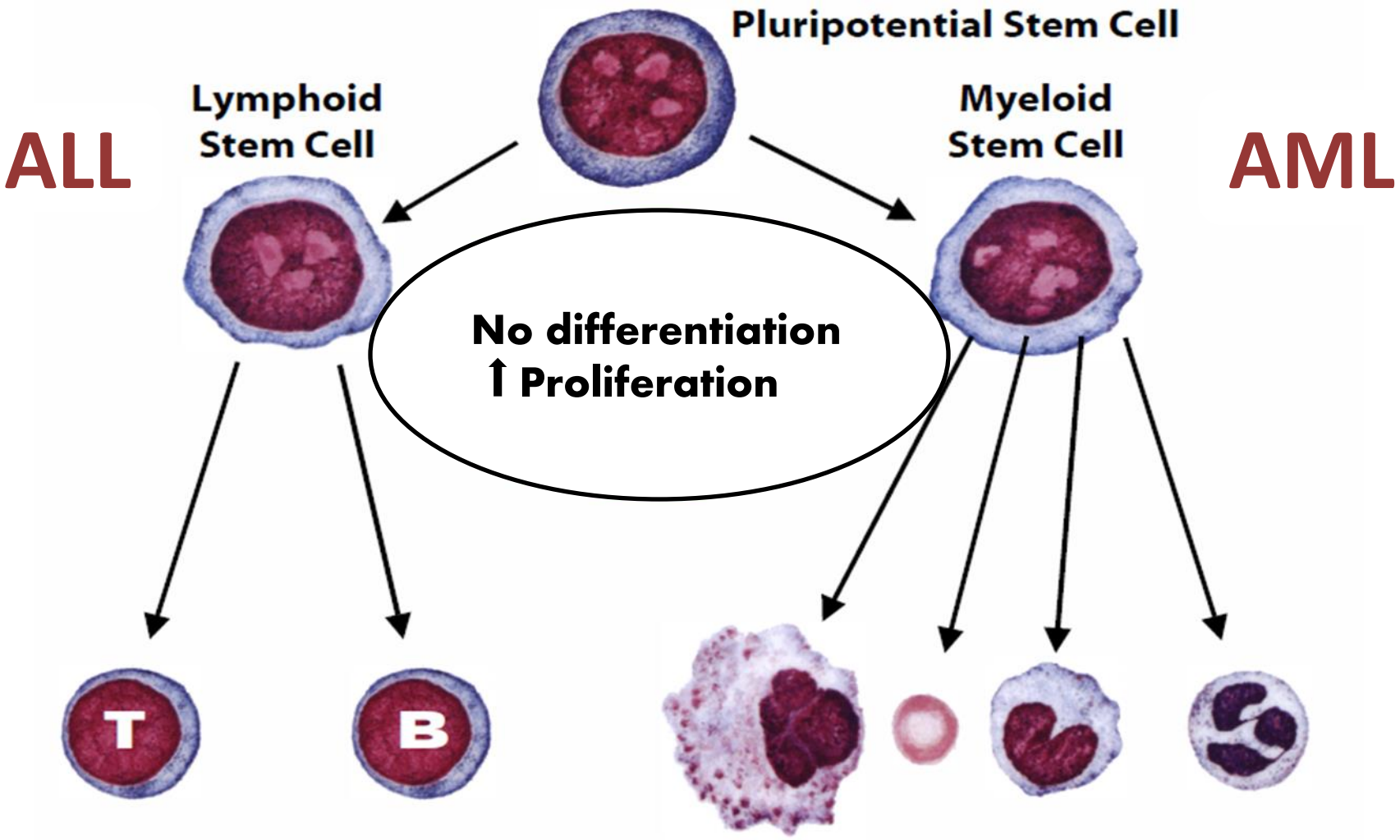
Genetic alteration in the immature precursors

Block of differentiation ,Enhanced proliferation & Decreased apoptosis





PATHOGENESIS



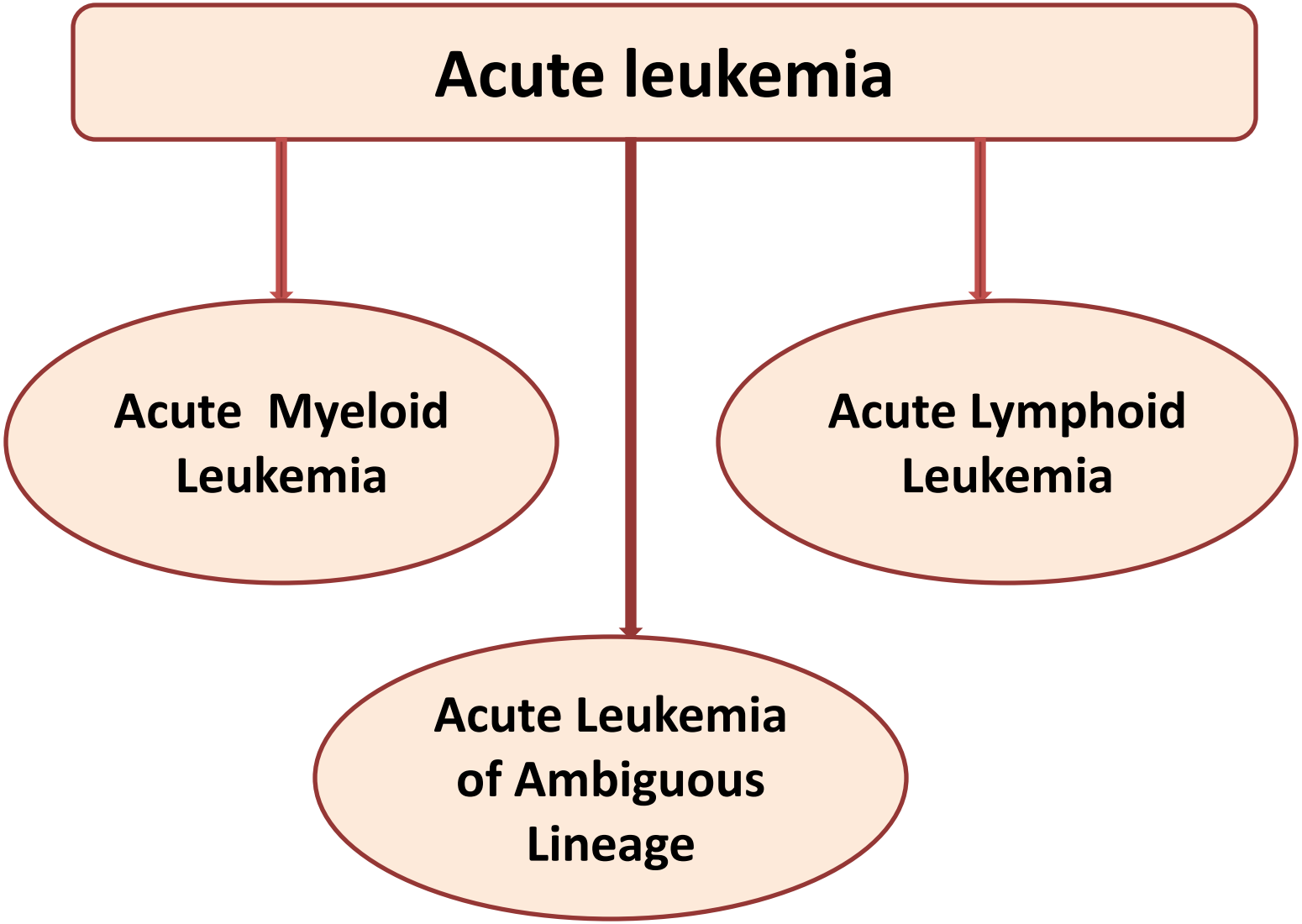
Epidemiology

- AL represent about 8% of neoplastic disease & cause about 4% of malignancy related deaths !

- AML has an incidence of 2 – 3 per 100 000 per year in children, rising to 15 per 100 000 in adults.

- ALL has an incidence of 30 per million & represent about 76% of childhood leukemia .

General Classification

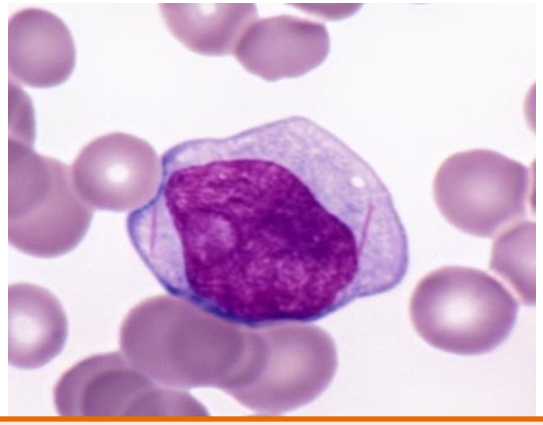


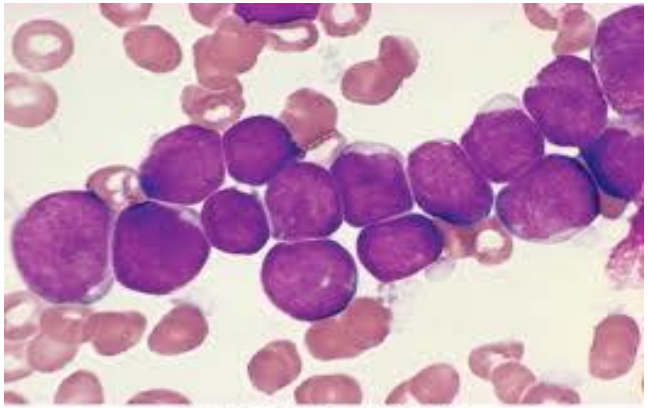
Basis of Classification

1. **Clinical history** (Previous therapy)
2. **Morphology**
3. **Flow cytometry**
4. **Chromosomal Karyotyping**
5. **Molecular study**

1- Light microscopy (blood smear, bone marrow aspirate & biopsy)

- Blast count : it should be >20% out of the total cells
- Blast morphology :





Myeloblast:

-Size: medium-Large
-Nucleous: round, oval or irregular
-Nucleolus: prominent
-Cytoplasm: abundant, granular

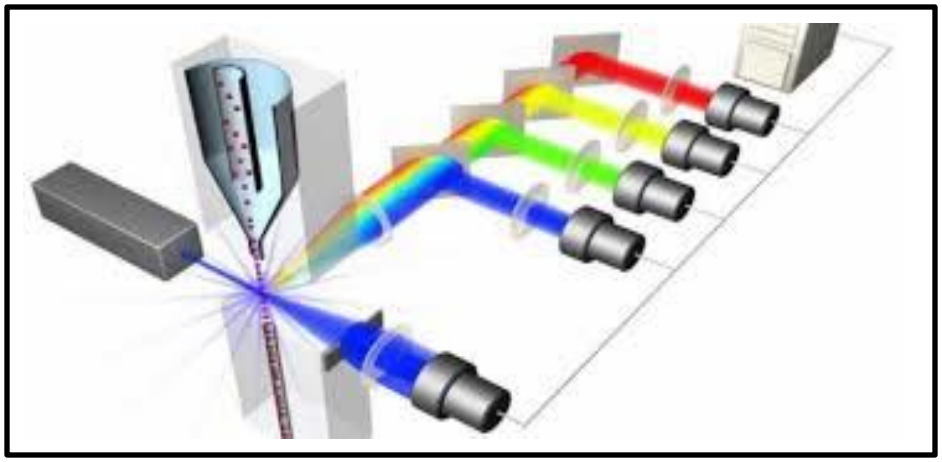
Auer rods is characteristic

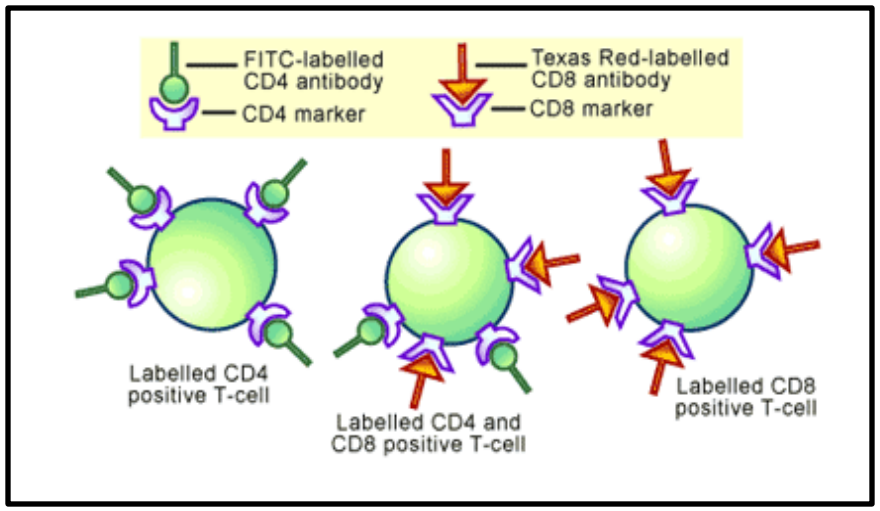
Lymphoblast:

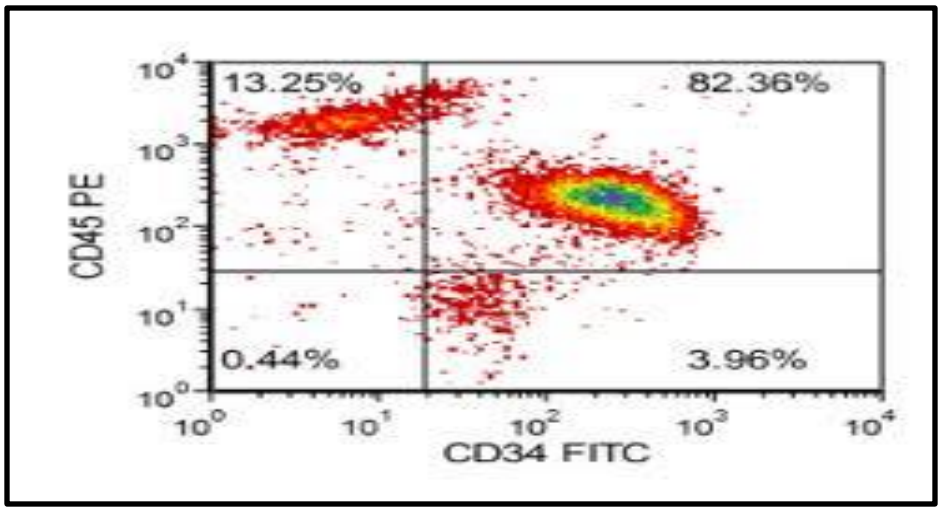
- Size: small- medium
- Nucleous: round
- Nucleolus: not prominent
- Cytoplasm: scanty ,agranular
  may be vacuolated

2-Flow cytometry:

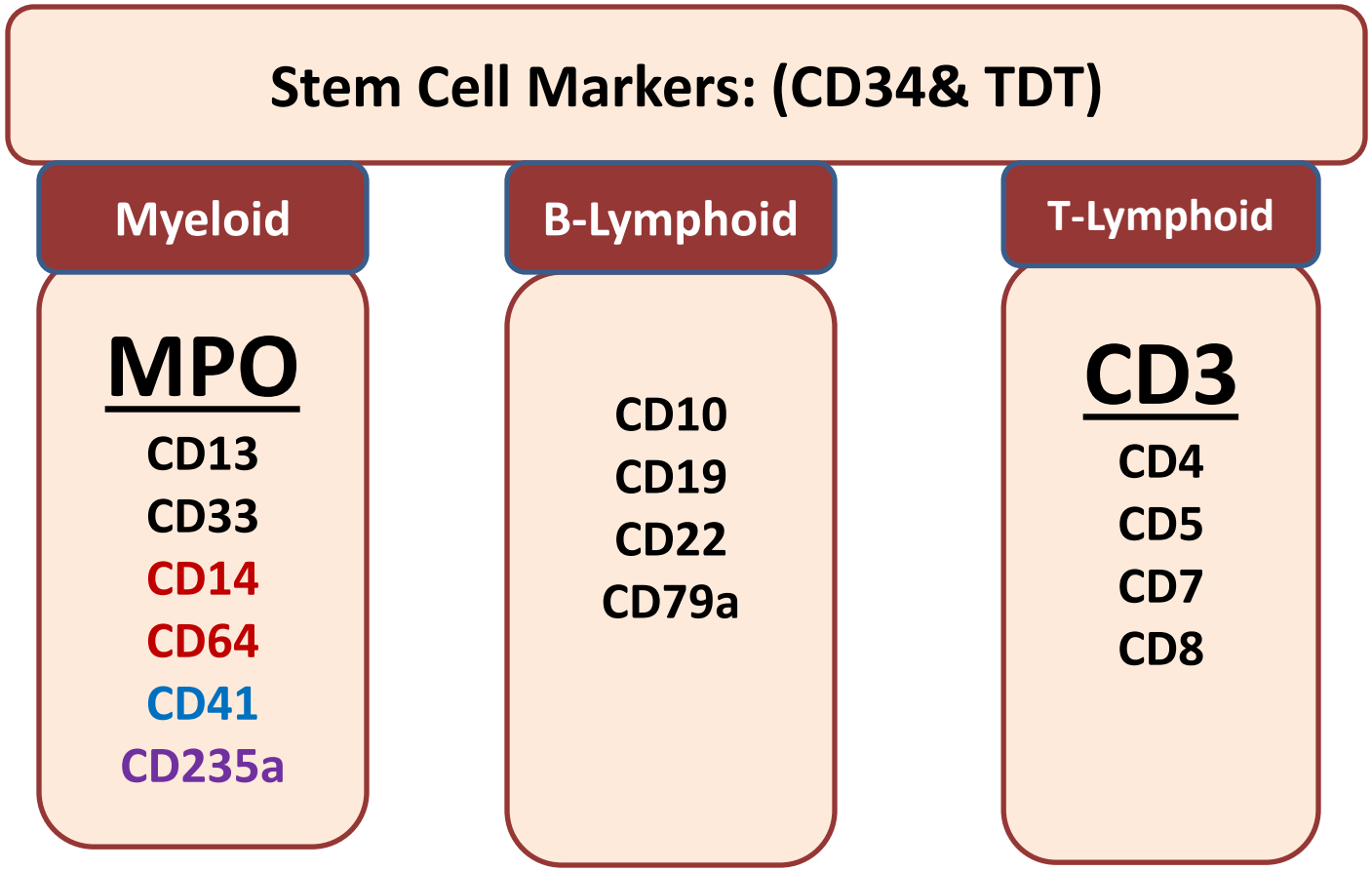
Laser based technology allows for cells counting & detection of their surface &cytoplasmic markers by suspending them in a stream of fluid followed by analysis through electronic system.





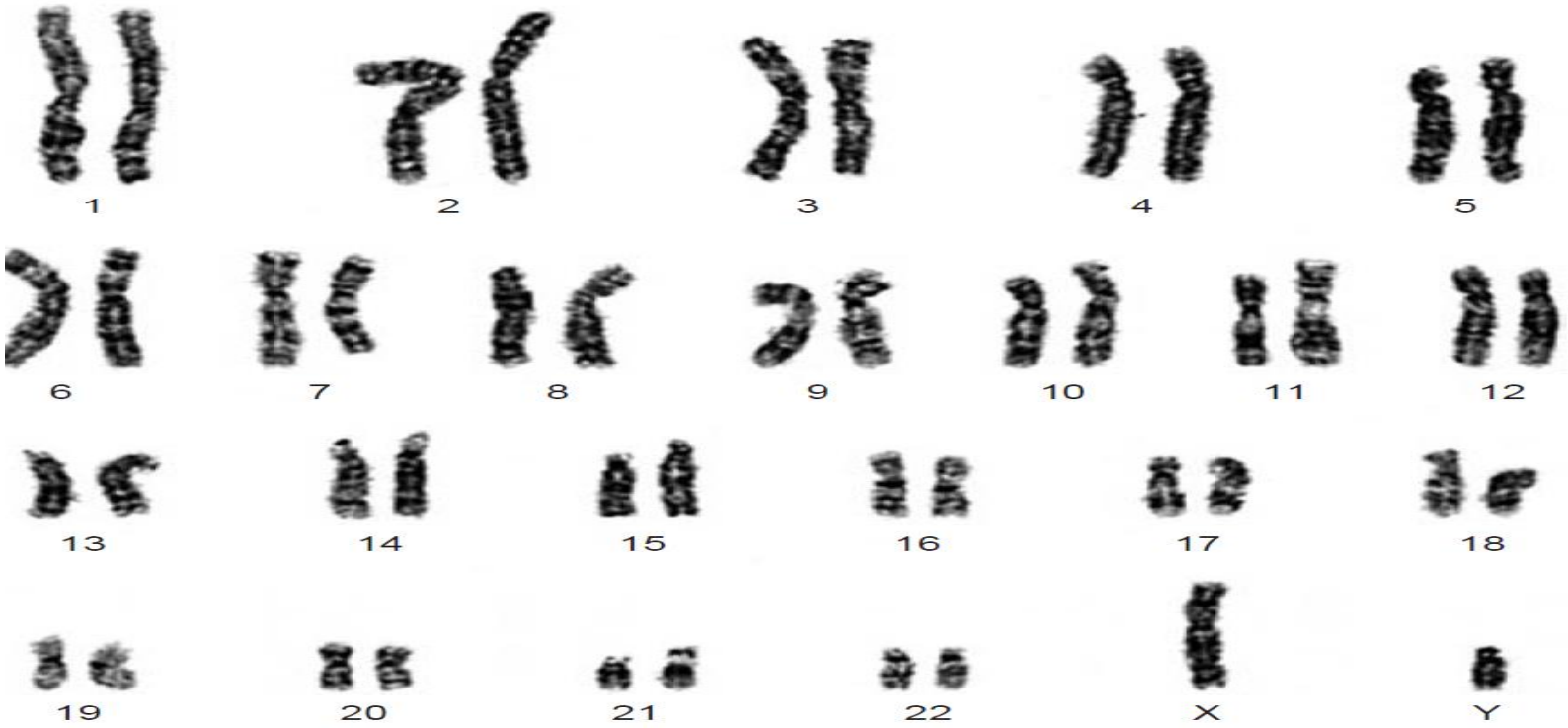


Basis of Classification



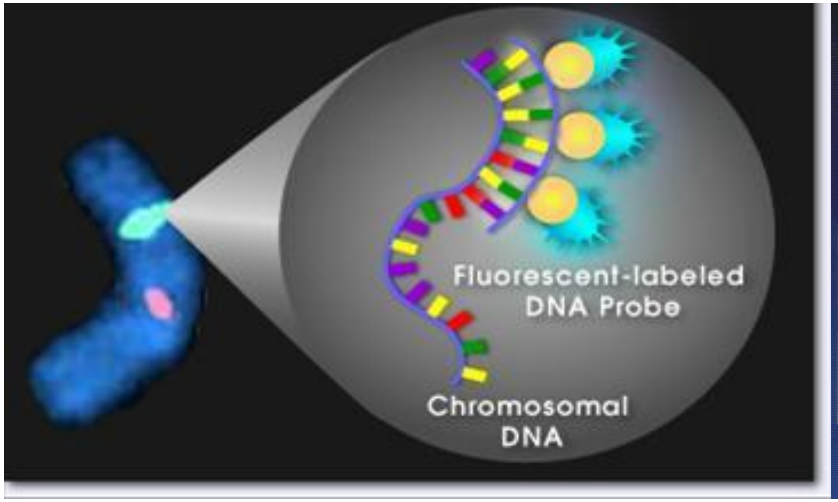
3-Chromosomal Karyotype

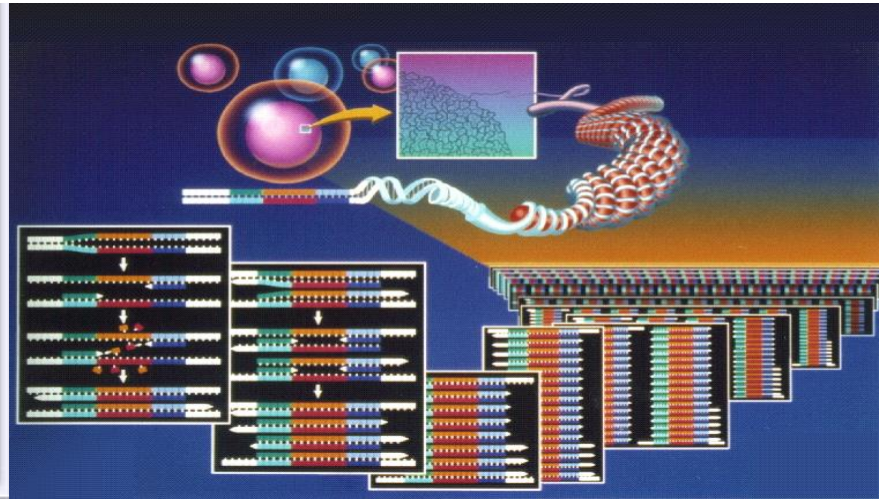
Set of the chromosomes from one cell during metaphase to study the numerical(deletion &trisomy) and structural (translation &inversion) abnormality



4- Molecular studies:

Several techniques used to detect and localize the presence or absence of specific DNA sequences on chromosomes





Fluorescent In-Situ Hybridization (FISH)

Polymerase Chain Reaction (PCR)

Recurrent genetic abnormalities

AML

Karyotype	Molecular
t (8;21)	AML1-ETO
t (16;16) or inv(16)	CBFB-MYH11
t (15;17)	PML-RARA
t (9;11)	MLLT1-MLL

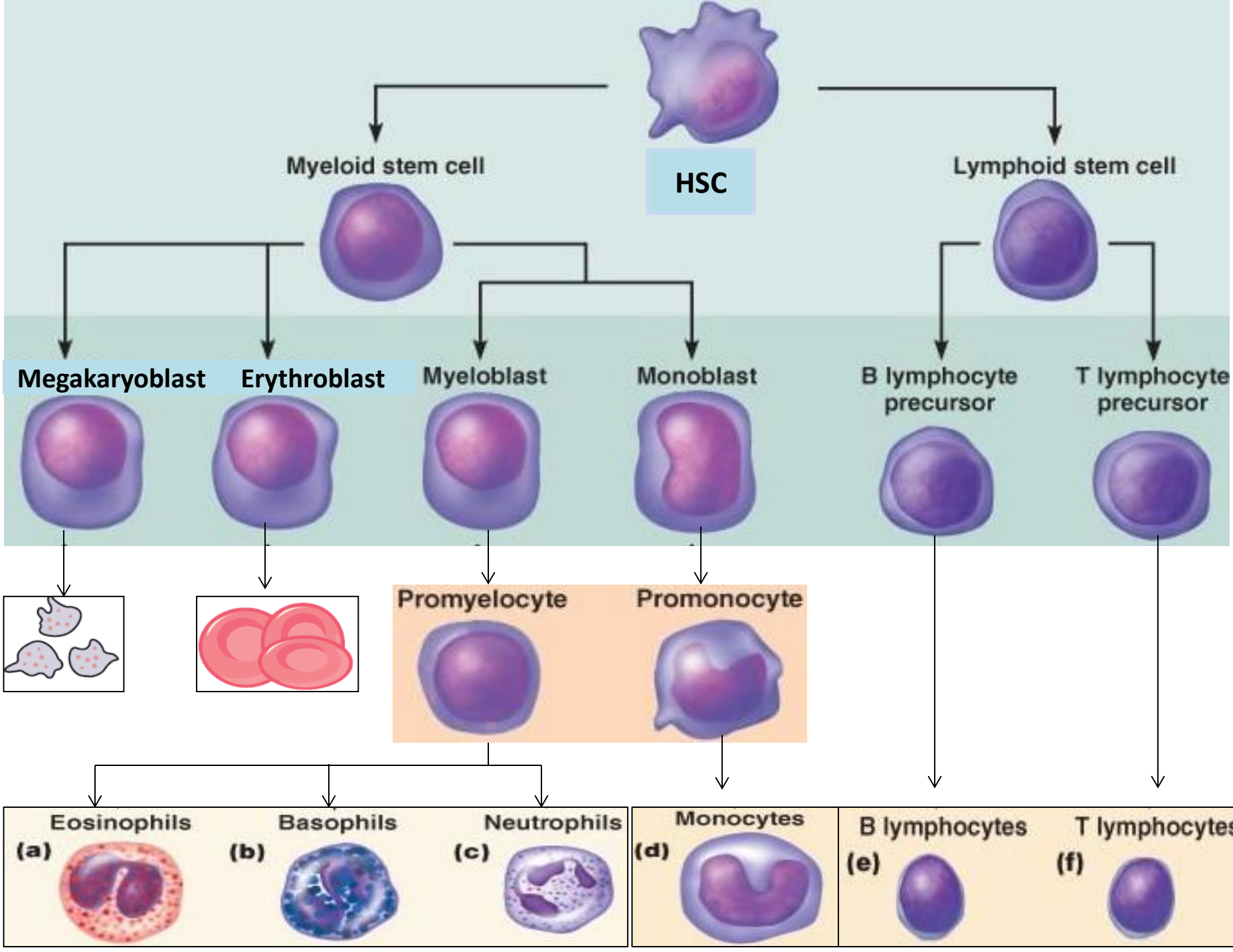
ALL

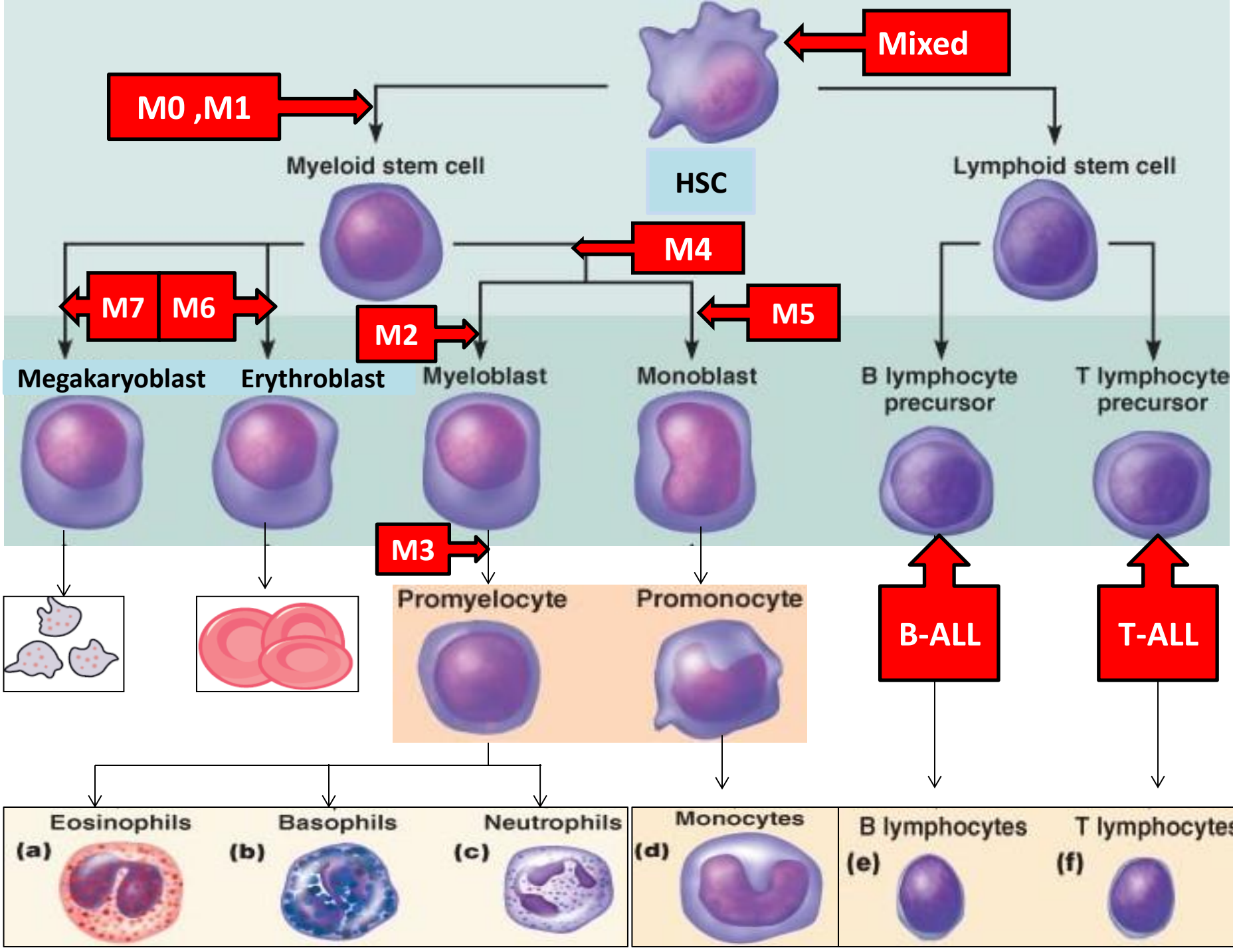
Karyotype	Molecular
t (9;22)	BCR-ABL1
t (4;11)	AF4-MLL
t (12;21)	ETV6-RUNX1
t (5;14)	IL3-IGH

ACUTE MYELOID LEUKEMIA

Acute Myeloid Leukemia

- Group of hematopoietic neoplasms caused by proliferation of malignant myeloid blasts in bone marrow and blood.
- The blast ≥20% or t(8;21) t (16;16) or t(15;17).
- More in Adults (do occur in infants!)
- Worse than ALL


HSC
Myeloid stem cell
Lymphoid stem cell
Megakaryoblast
Erythroblast
Myeloblast
Monoblast
B lymphocyte precursor
T lymphocyte precursor
Promyelocyte
Promonocyte
Eosinophils
(a)
Basophils
(b)
Neutrophils
(c)
Monocytes
(d)
B lymphocytes
(e)
T lymphocytes
(f)


Mixed
M0 ,M1
HSC
Myeloid stem cell
Lymphoid stem cell
M4
M7
M6
M2
M5
Megakaryoblast
Erythroblast
Myeloblast
Monoblast
B lymphocyte precursor
T lymphocyte precursor
M3
Promyelocyte
Promonocyte
B-ALL
T-ALL
Eosinophils
(a)
Basophils
(b)
Neutrophils
(c)
Monocytes
(d)
B lymphocytes
(e)
T lymphocytes
(f)

FAB Classification

- Based on morphology& flow cytometry

Subtype	Features	Genetics in WHO	Notes
Mo	Minimal differentiation		
M1	Without maturation		
M2	With maturation	t(8;21)	
M3	Promyelocytic	t(15;17)	DIC
M4	Granulocytic and monocytic	t or inv(16;16)	Gum hypertrophy
M5	Monoblastic (M5a) Monocytic (M5b)	t(9;11)	
M6	Erythroid		CD235a
M7	Megakaryocytic		CD41
M8	Basophilic		

AML Classification (WHO)

AML with recurrent genetic abnormalities

1- t(8;21)
2- t(16;16)
3- t(15;17)
Prognosis:
Good

Myelodysplasia related AML

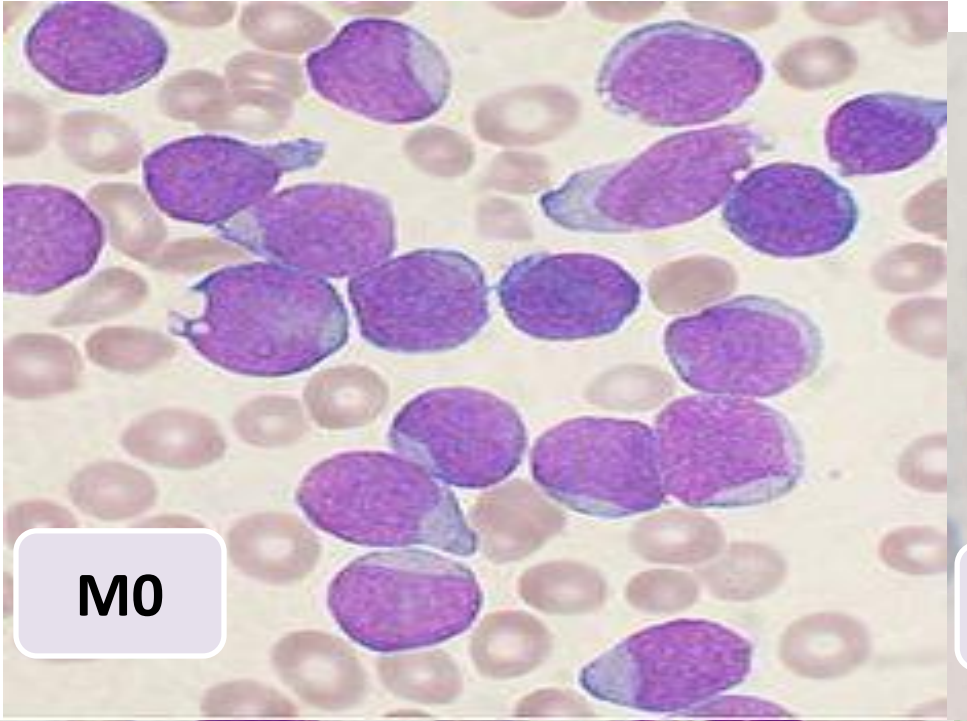
•Blasts≥ 20%
•Significant dysplasia
Prognosis:
poor

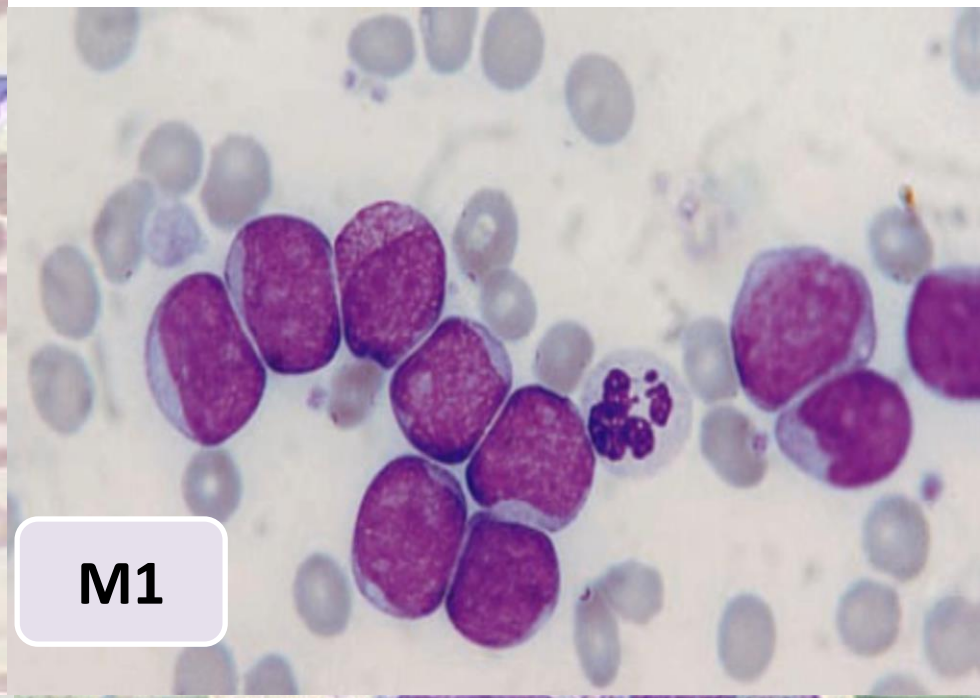
Therapy related AML

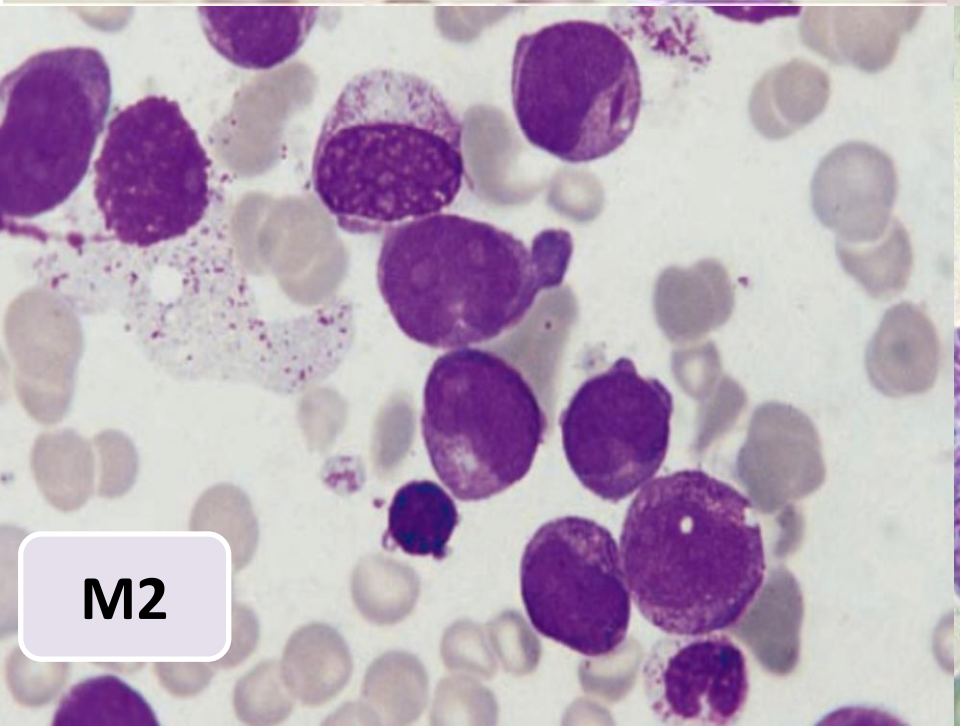
•Blasts≥ 20%
•Previous chemotherapy
Prognosis:
poor

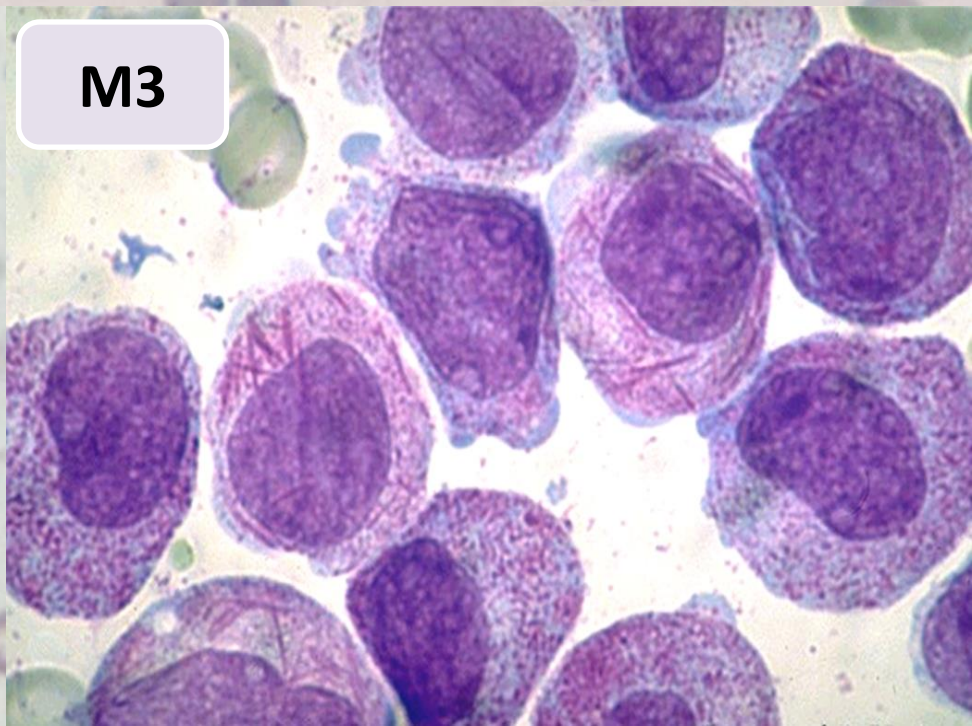
AML, not otherwise specified (FAB)

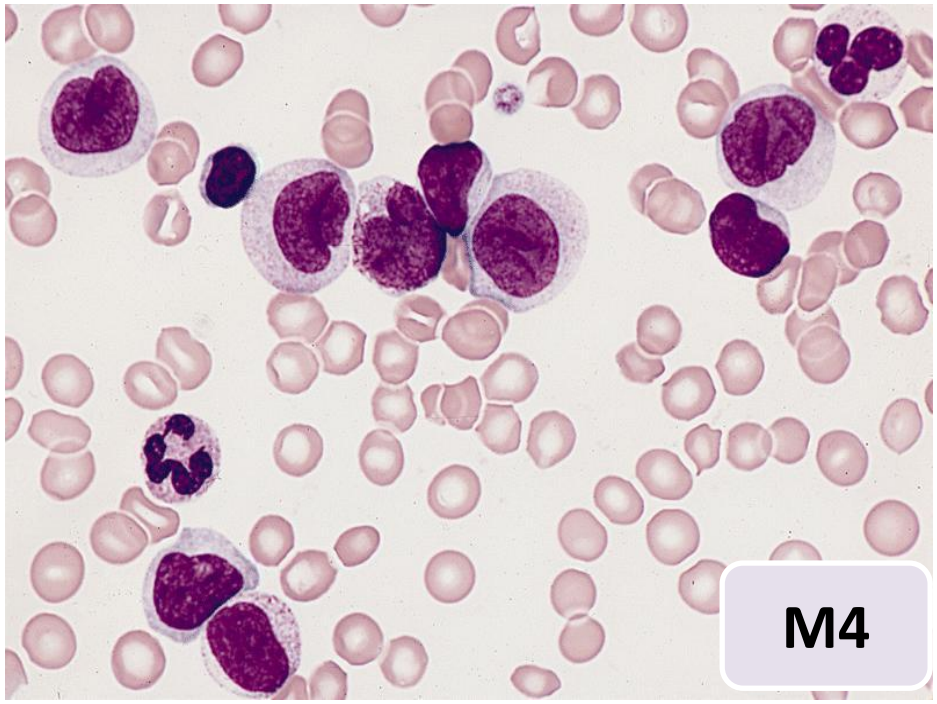
•Blasts≥ 20%
•Genetic: N
•No dysplasia
Prognosis:
Standard

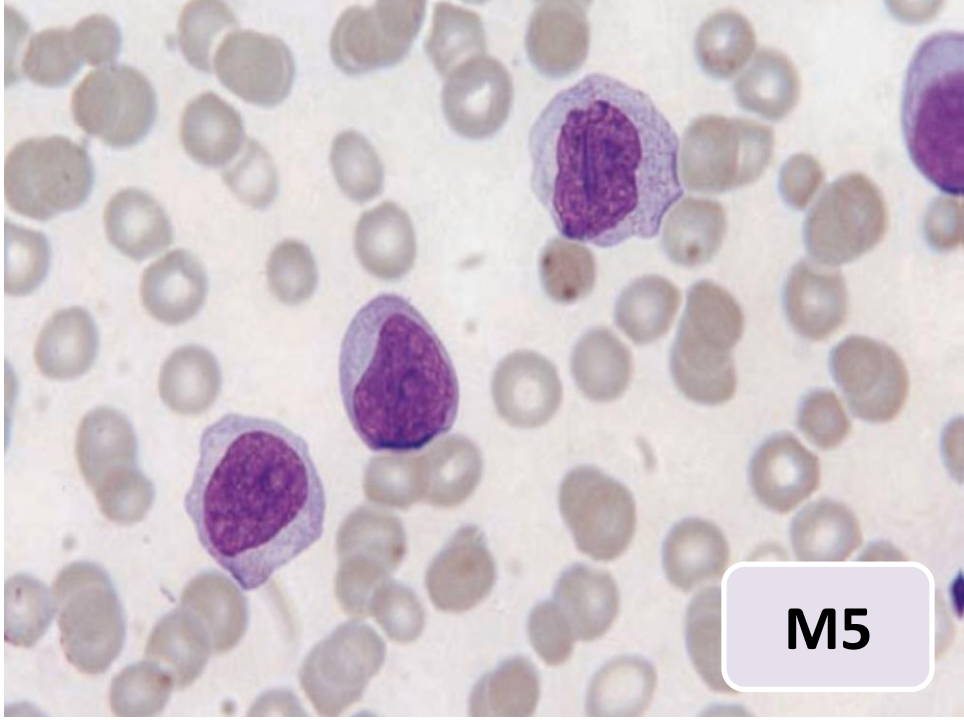

M0


M1

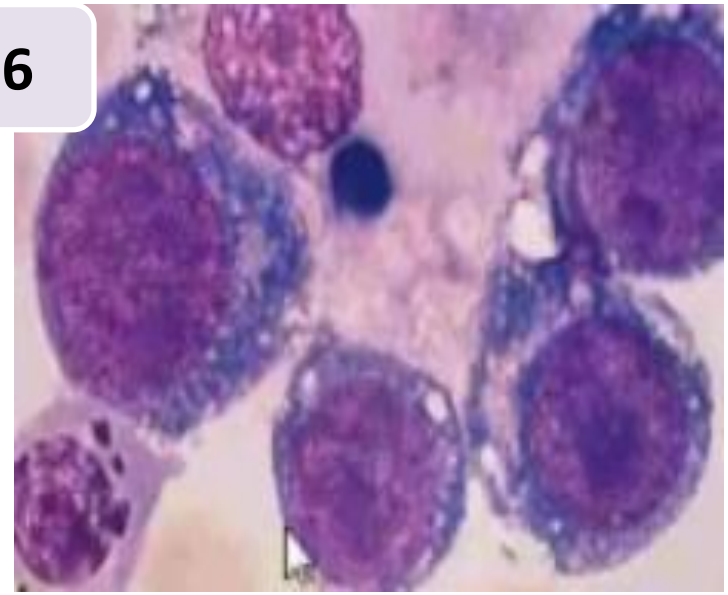

M2

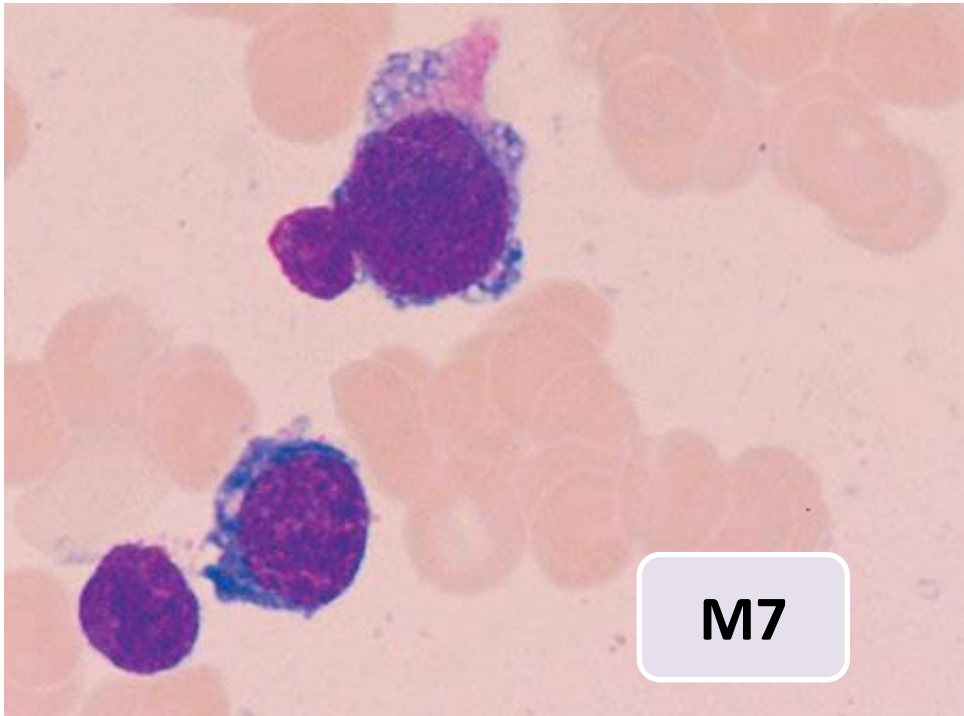

M3





M6





Clinical Features of AML

1-Pancytopenia:

↓WBC→ infection (fever ,septic shock)

↓Hb →anemia (fatigue , headache , pallor ,SOB….)

↓platelets →bleeding (bruises , epistaxis ,menorrhagia…)

Acute onset

2-Organ infiltration:

- Hepatosplenomegally.
- Lymphadenopathy (rare)
- Myeloid sarcoma
- Gum hypertrophy
- CNS disease

More with Acute Monoblastic Leukemia

Clinical Features of AML

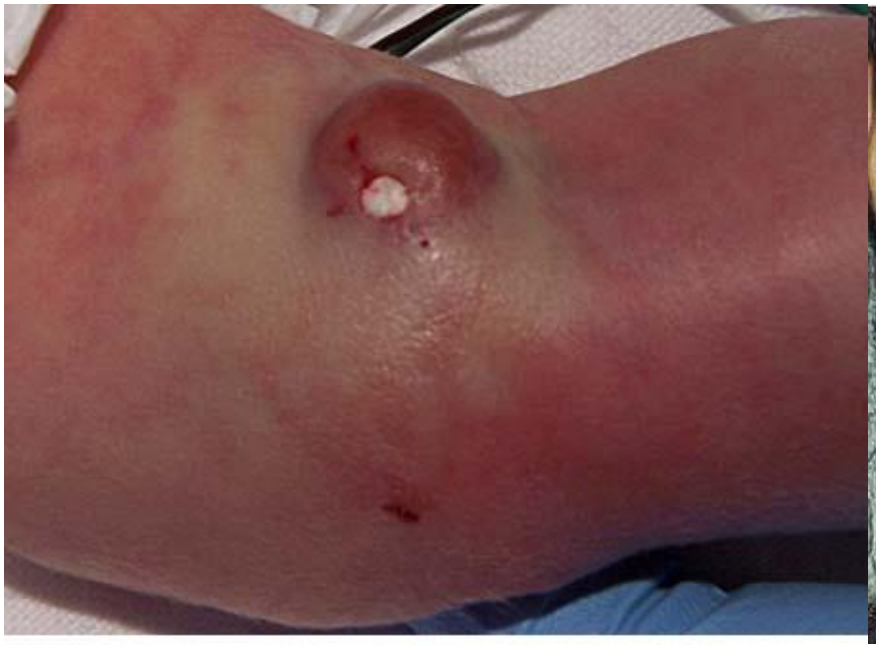
3-Leucostasis (increased blood viscosity)

4-Disseminated Intravascular Coagulation (DIC):

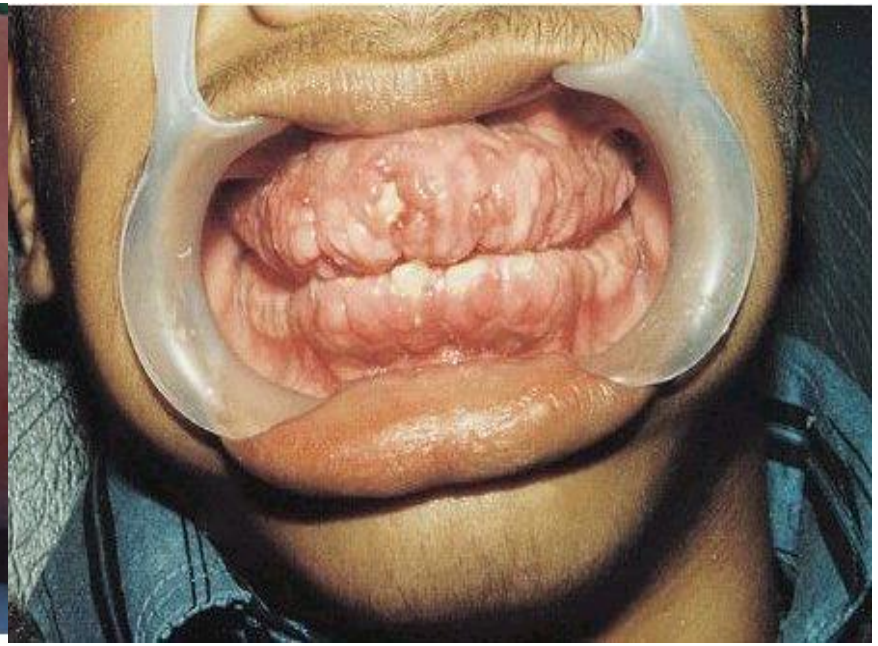
Widespread activation of coagulation system leading to intravascular fibrin deposition &consumption of platelet and coagulation factors which can be manifested as bleeding (85%) or thrombosis (15%)

More with Acute Promyelocytic leukemia (M3)

Clinical Features of AML



Myeloid sarcoma

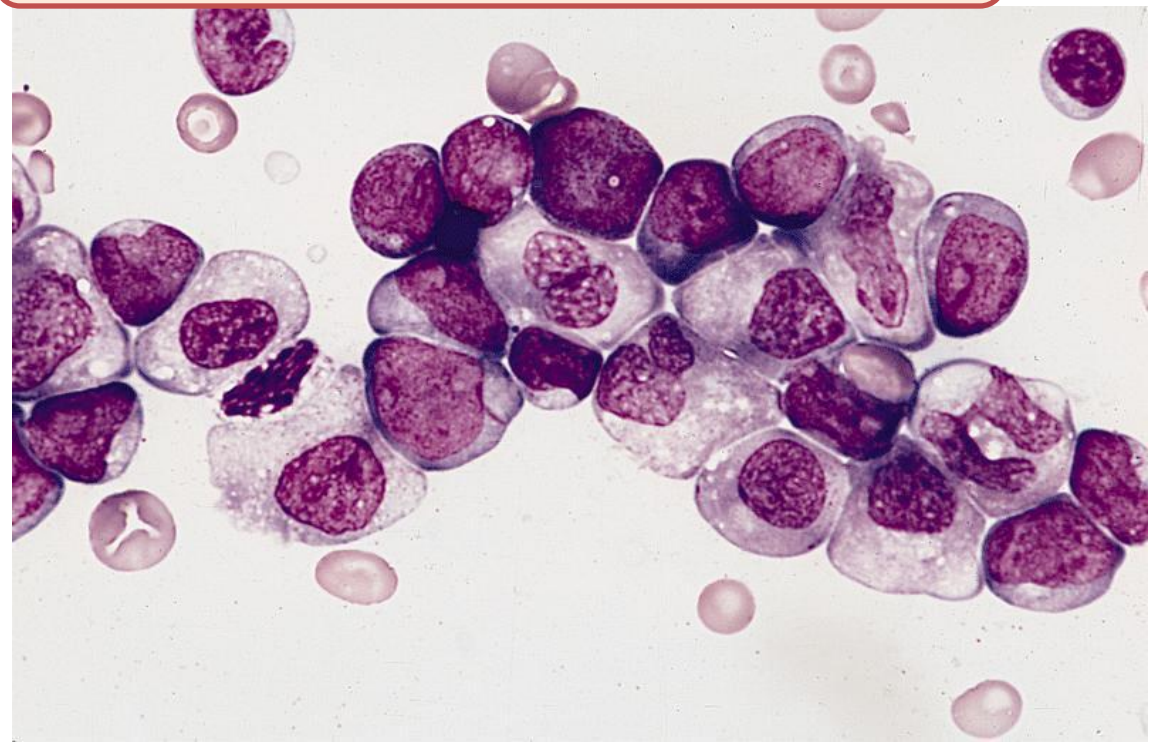


Gum hypertrophy

Case Study

- 65 years old male presented to ER with fatigue ,fever and nose bleeding for 2 weeks.
- O/E : moderate hepatosplenomegaly & multiple bruises.
- CBC : WBC :40 $x10^9/L$ HB: 7g/dL PLT: 51 $x10^9/L$

Blood smear & bone marrow:



?

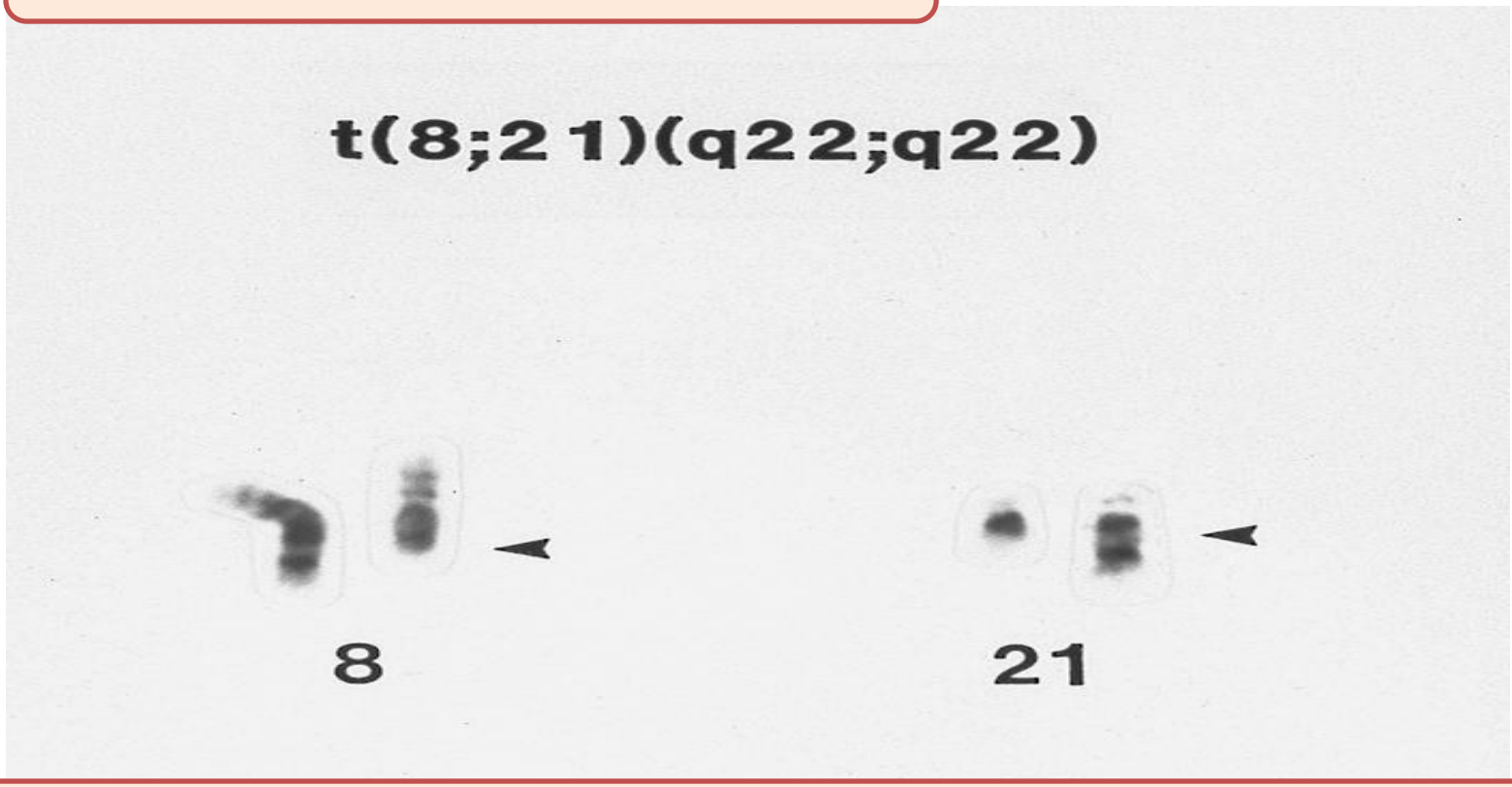
Flow cytometry :

The blast are positive for CD34 ,CD13,CD33,CD117 and MPO

They are negative for CD3,CD10,CD19&CD79a

AML with maturation (M2) (FAB)

Karyotype :



The final diagnosis: AML with t(8;21) (WHO)

Prognosis and treatment

Better prognosis:

- Genetics: t(8;21), inv(16;16) or t(15;17)
- Age: < 60 years
- Primary better than secondary

Treatment

- Chemotherapy:
  - AML: M0-M8 but not M3 (same protocol)
  - AML: M3 (ATRA or arsenic)
- Stem cell transplantation

ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

Acute Lymphoblastic Leukemia (ALL)

- Acute leukemia characterized by proliferation of malignant lymphoid blasts in bone marrow and blood.
- B and T cells
- More common in Children
- Better than AML

Clinical Features of ALL

1-Pancytopenia:

↓WBC→ infection (fever ,septic shock)

↓Hb →anemia (fatigue , headache , pallor ,SOB….)

↓platelets →bleeding (bruises , epistaxis ,menorrhagia…)

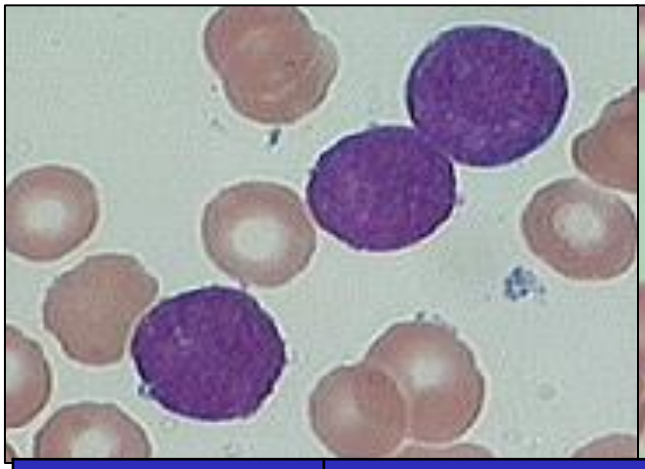
Acute onset

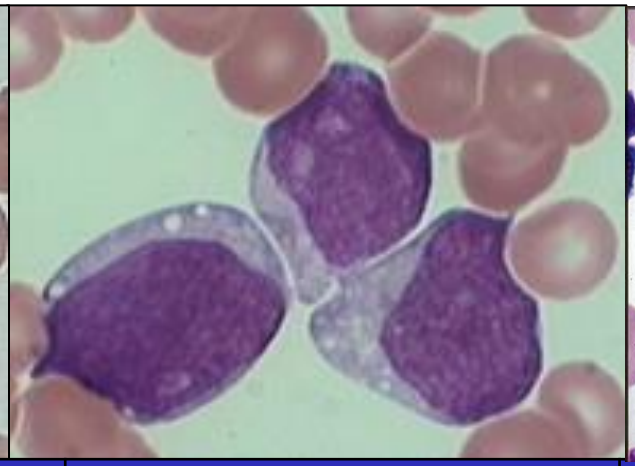
2-Organ infiltration:

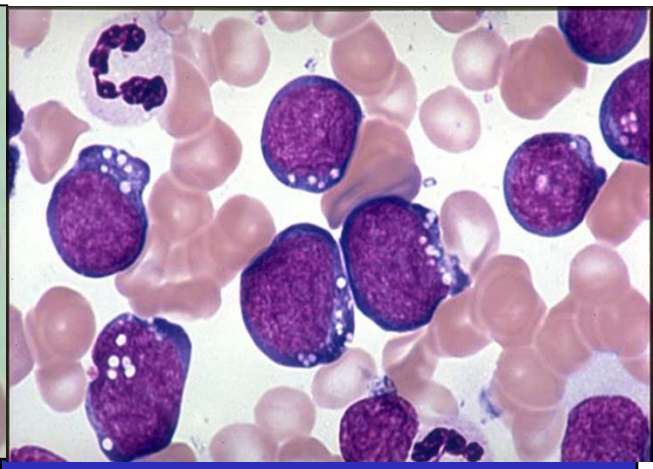
- Lymphadenopathy (very common)
- Hepatosplenomegally.
- testicles involvement
- CNS disease
- Mediastinal mass

Characteristic for T-ALL

Morphological subtypes (FAB)







	L1	L2	L3 Burkitt's
Morphology	Homogenous	Heterogeneous	Homogenous
Size	Small	Variable	Small
Cytoplasm	Little	More	Vaculated
Nucleoli	Not prominent	Prominent	Prominent
Genetics	Variable	Variable	t(8;14) cmyc

Immunophenotypic Subtypes (WHO)

	B cell	T cell
Markers	CD19,CD10,CD79a	CD3
Percentage	80%	20%
Age	Younger	Older
Clinical	-------	Mediastinal mass CNS relapse
WBC count	Less	Higher
Prognosis	Better	Worse
Genetics	t(9;22),t(4;11),t(12;21)	-------

L3 (Burkitt's) represents mature lymphoid neoplasm so it is a type of lymphoma not Acute lymphoblastic leukaemia

Prognosis &treatment

	Better	Worse
Age	2 - 10 yrs	<2 - >10 yrs
Gender	F	M
WBC count	Low	High
Cell type	B cell	T cell
B-ALL phenotype	Common	Others
B-ALL genetics	Hyperdiploidy t(12;21)	Hypodiploidy t(9;22)
CNS involvement	No	Yes

Treatment:

- Chemotherapy (high cure rate)
- Stem cell transplantation

Remember !

- Acute leukaemia is a fatal neoplastic condition
- 20% or more blasts = Acute leukaemia
- Diagnosis requires special investigations
- Auer rods = AML
- AML M3 = DIC &target therapy
- Gum hypertrophy = mostly M4 or M5,
- Mediastinal = T-ALL

Remember !

- Subtypes of AML (M0-M8) + cytogenetic abnormalities
- Subtypes of ALL (T or B cell)
- Main lineages markers are MPO, CD19 and CD3
- Stem cell markers are CD34,TDT
- FAB classification based mainly on morphology
- WHO classification focused more on genetics